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COOLEY'S ANEMIA: PREVENTION THROUGH UNDERSTANDING

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Division of Blood Diseases and Resources
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What are Cooley's anemia, Mediterranean anemia, and thalassemia major?

These terms refer to a severe, inherited form of anemia first described by Dr. Thomas Benton Cooley, an American pediatrician, in 1925. The condition is more exactly called beta thalassemia major. The word thalassemia is based on the Greek word *thalassa*, which means "sea." Most of those in the United States who have the disorder are descendants of families who originally came from countries around the Mediterranean Sea, particularly Italy and Greece, which also explains the occasional use of the term "Mediterranean anemia" to refer to beta thalassemia major. Many diseases are also named after the physicians who first described them, which explains the more commonly used term "Cooley's anemia."

Are there other forms of this disorder?

Yes. Cooley's anemia refers specifically to beta thalassemia major. In addition to Cooley's anemia, there are several other forms of thalassemia, which include beta thalassemia minor and alpha thalassemia. Alpha thalassemia is not as common in the United States as are beta thalassemia major and minor; it is the more frequently found form in the Far East. Cooley's anemia also occurs in persons of Middle Eastern, Southeast Asian, and African descent and occasionally in other ethnic groups.

CAUSE

What causes Cooley's anemia?

The basic defect in Cooley's anemia is a decrease in the rate at which one or more of the globin chains of hemoglobin are made by the body. (Hemoglobin is the protein pigment of the red blood cells that carries oxygen to the tissues; it is made up of heme, which contains iron, and four globin chains, of which there are at least four kinds, designated *alpha, beta, gamma,* and *delta.* There are several types of hemoglobin, which are determined by the specific combinations of the four different kinds of globin chains in the hemoglobin.)

How do various forms of thalassemia differ?

In Cooley's anemia, which is the severe form of the disorder, there is an insufficient amount of the beta globin chains of hemoglobin. In alpha thalassemia, there is an insufficient amount of the alpha globin chains of hemoglobin.

In beta thalassemia minor, or thalassemia trait, which is a mild form of the disorder and which is compatible with an entirely normal life, there is an increase in the amount of one of the types of hemoglobin, called hemoglobin A_2. This type of hemoglobin is normally present in only limited amounts in the red blood cells of the adult. There are also certain abnormalities of the red blood cells, but these abnormalities vary considerably and, in some cases, may be absent.

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What determines whether Cooley's anemia will be inherited?

Cooley's anemia may be inherited if both parents have the gene for thalassemia. If each parent has thalassemia trait, there is a one-in-four chance with each pregnancy that the child born to such parents will have Cooley's anemia; there is a two-in-four chance that the child will have the trait and a one-in-four chance that the child will be normal. Because these chances also apply for each succeeding pregnancy, the family would not necessarily have the probable distribution of a fourth of the children with Cooley's anemia, half with thalassemia trait, and a fourth normal; all of the children could have Cooley's anemia, all could have thalassemia trait, or all could be normal.

If one parent has beta thalassemia trait and the other parent is normal, each child born will have a one-in-two chance of having the trait and a one-in-two chance of being normal; the couple could not have a child with Cooley's anemia. Cooley's anemia can occur only if both parents have some form of thalassemia.

SYMPTOMS

What are the symptoms or signs of Cooley's anemic?

The earliest signs, which are similar to those for any other type of anemia, are paleness, weakness, irritability, and failure to thrive. Fever, feeding problems, diarrhea, and other gastrointestinal symptoms may be present.

When do the symptoms of Cooley's anemia develop?

An infant with Cooley's anemia appears normal at birth. Signs of the disease first develop a few months after birth and become progressively more severe.

EFFECT ON VICTIMS

How does the disease affect its victims?

Because the red blood cells are defective and do not contain appropriate amounts of hemoglobin, children with Cooley's anemia have a complicated group of clinical problems. The red blood cells are pale, thin, and misshapen; most of them are very small, but an occasional one may be large and thin. These cells do not survive for very long; they are fragile and break down within a few weeks instead of lasting for four months, which is the lifetime of normal red blood cells.

The need for new red blood cells to replace those that are damaged causes the bone marrow cavity, where the cells are made, to expand remarkably. This expansion results in widening of the bone marrow spaces and thinning of the bones, especially the bones of the skull and face. Because of this, children with Cooley's anemia have a characteristic appearance, with prominent cheek bones, slanting eyes, overgrowth of the upper jaw, jumbled upper teeth, and an overbite. The bones are thinner than in a normal child, and they fracture easily.

Are these fragile, short-lived red blood cells harmful to the body in other ways?

Yes. As red blood cells break down, their components, which are now waste products, are eliminated through a process that takes place mainly in the spleen and liver. Since the breakdown of red blood cells in Cooley's anemia is accelerated, there is more work for the spleen and liver to do. Consequently, these organs become huge in children with Cooley's anemia and often do not function properly. Although of enormous size, the spleen may fail in its critical function of protecting the body against infection. Enlargement of the spleen also leads to a condition called hypersplenism, in which the destructive process in the spleen is exaggerated, with the result that platelets, white blood cells, and transfused (normal) red blood cells are broken down prematurely.

What happens to the iron from the accelerated breakdown of the red blood cells?

The iron that is released from the accelerated destruction of red blood cells remains in the body and is deposited in excess in all the tissues, especially the heart, liver, endocrine glands, and skin. Excess iron, or iron overload, in the heart and liver interferes with the functions of these organs; excess iron in the endocrine glands can cause diabetes mellitis, calcium deficiency, poor thyroid function, and impairment of sexual function.

Is the child's growth affected?

Yes. Growth tends to be slower than normal. With newer forms of treatment, however, it appears that children who have Cooley's anemia may be able to grow normally.

Is Cooley's anemia fatal?

Yes. Without treatment, the victims of Cooley's anemia die in early childhood, usually as a result of overwhelming infection. Although blood transfusions may be used to treat the symptoms of anemia, patients who receive only blood transfusions eventually die young from complications caused by deposits of excess iron in the heart muscle. Life is being extended, however, by treatment with a combination of blood transfusions and the removal of excess iron by the use of a drug or chemical known as an "iron chelator" started at the time of early diagnosis.

TREATMENT

What is the usual form of treatment?

There are two important aspects to the modern treatment of Cooley's anemia. First, transfusions of packed red blood cells are used to relieve the anemia and its effects. These transfusions diminish the overactive production of red blood

cells by the bone marrow, which prevents the bony abnormalities described above. Eventually, however, these transfused red blood cells break down and their iron remains in the organs of the body. Second, an iron chelator is used to prevent such deposits of excess iron in the body. A solution of deferoxamine, known also as desferrioxamine mesylate, DFOM, or Desferal®, the agent most commonly used, may be infused just under the skin over a period of 8 to 12 hours, usually at night; the flow of the infusion is maintained by the use of a small, light, portable pump. The transfusion and chelation treatments together represent a major scientific advance in the treatment of Cooley's anemia.

Removal of the spleen becomes necessary when the spleen becomes enlarged and overactive. Since young patients without spleens are highly susceptible to infections, they should be given the recently developed vaccine against pneumococci. The functions of the heart, liver, and endocrine glands must also be checked frequently and carefully so that treatment can be given as needed.

Are there any side effects associated with treatment?

The side effects of transfusions fall into two groups. First, there are the dangers that go along with transfusions, which require constant guarding against possible human errors; careful typing and cross-matching for major and minor blood groups; and removal of white blood cells by means of washing, freezing, or centrifuging blood before it is transfused. Second, the most serious side effect is the storage

of iron in vital organs as a result of the large amounts of transfused blood needed for treatment. As mentioned above, this side effect can be prevented by transfusions together with an iron chelator, such as deferoxamine, which combines with the iron and helps the body get rid of excess iron through the urinary system. Treatment with deferoxamine seems to have remarkably few side effects when it is injected under the skin.

What is the life expectancy of patients who receive proper treatment?

The life expectancy of patients who are treated with modern methods from early infancy is at present unknown, since the successful removal of excess iron by treatment with iron chelators is a recent medical advance.

Where can I find out about medical help and where Cooley's anemia can be diagnosed and treated?

Your own family physician should be able to refer you to medical facilities where diseases of the blood are treated. Other sources of referral are your local and state health departments and your local and state medical societies. You may also wish to contact the Cooley's Anemia Foundation, Incorporated, Graybar Building, Suite 1644, 420 Lexington Avenue, New York, New York 10017, telephone (212) 697-7750, or the Ahepa (American Hellenic Educational Progressive Association) Cooley's Anemia Foundation, 1422 K Street, N.W., Washington, District of Columbia 20005, telephone (202) 628-4974.

PREVENTION

Can Cooley's anemia be prevented?

The only way to prevent Cooley's anemia at the present time is to prevent the birth of affected infants. The first step in such prevention takes place when both parents are identified as carriers of thalassemia trait or as having some other form of thalassemia and are thus at risk for having a child with Cooley's anemia. The possibility of the trait can be suspected when laboratory tests show the presence of small red blood cells and an elevated amount of a type of hemoglobin called hemoglobin A_2. The diagnosis is confirmed by ruling out iron-deficiency anemia and by finding the trait in other members of the family.

Once it has been established that both potential parents have the trait or some other form of thalassemia, the second step is counseling. In counseling, trained health-care workers inform the potential parents of the risks involved and allow them to decide whether they wish to take the one-in-four chance of having a severely affected infant.

Is there a prenatal test for the detection of Cooley's anemia?

A prenatal test for Cooley's anemia is available, but it is usually not the regular form of prenatal test (amniocentesis) used to determine Down's syndrome (mongolism), certain congenital defects, or the sex of the fetus, for example. Instead

of being able to use the fluid that surrounds the fetus, the physician usually requires a small sample of blood that has to be taken directly from the fetus by a procedure known as fetoscopy. A physician especially trained in the use of this delicate technique places a small tube inside the amniotic sac and withdraws from the fetus a sample of blood through a small needle at the end of the tube. The blood of the fetus is then separated from the blood of the mother and tested for the production of beta globin chains. In certain cases, amniocentesis can be used instead of fetoscopy.

If a woman known to be at risk for bearing a child with Cooley's anemia becomes pregnant, she may choose to have this prenatal test, with the option of therapeutic abortion if the fetus is found to be severely affected.

Where can I find out about genetic counseling services?

Any major medical center where blood diseases are treated should have such services available or be able to refer you to where they can be obtained. The Cooley's Anemia Foundation, Incorporated; the Ahepa Cooley's Anemia Foundation; your local chapter of the National Foundation-March of Dimes; or the National Clearinghouse for Genetic Diseases of the Health Services Administration, United States Public Health Service (1776 East Jefferson Street, Rockville, Maryland 20852, telephone 301/279-4642), could also refer you to a source of genetic counseling services.

RESEARCH

What kind of research is currently being done on Cooley's anemia?

Scientific research on Cooley's anemia and similar genetic diseases is sponsored by the National Heart, Lung, and Blood Institute, the National Institute of Arthritis, Metabolism, and Digestive Diseases, the National Institute of General Medical Sciences, and other Institutes of the National Institutes of Health, as well as by a number of voluntary organizations. Important in basic research are studies of the genes and how they function. Current clinical research is concerned with improving techniques for transfusion therapy, iron chelation therapy, and prenatal diagnosis. Other research needs are for a simple, dependable screening test for the thalassemia trait and for easy and efficient ways to do screening and counseling.

Has bone marrow transplantation been successful in the treatment of Cooley's anemia?

Research is now being done on the possibility of using bone marrow transplantation in the treatment of Cooley's anemia. Although current research in this area is restricted to the use of experimental animals, it is possible that this form of treatment will be attempted for patients, on an experimental basis, in the future.

amniotic sac—The sac, within the uterus, containing the amniotic fluid and the fetus.

alpha globin chain—One of the chains of amino acids in hemoglobin; each normal hemoglobin molecule in an adult contains two alpha globin chains and two beta globin chains.

beta globin chain—Another chain of amino acids in hemoglobin; each normal hemoglobin molecule in an adult contains two beta globin chains and two alpha globin chains.

blood typing and cross-matching—Before a transfusion can be given, the type of blood, of which two major groups are ABO and Rh, from both donor and recipient must be determined. Donor's blood that is the same as (compatible with) that of the patient (recipient) must then be cross-matched by mixing the donor's red blood cells with a sample of the recipient's serum and *vice versa*. If the cells in these mixtures do not clump, the transfusion may be administered safely.

bone marrow—The tissue in the interior cavities of bones that produces the cells of the blood.

carrier—A person whose chromosomes contain, or "carry," both an abnormal gene, which is not generally expressed, and a normal gene. Some abnormal genes can be detected by laboratory tests.

chromosomes—Fine, threadlike structures in the cell nucleus that contain the genes.

Cooley's anemia—The commonly used name for beta thalassemia major, which is sometimes also called "Mediterranean anemia."

DNA (deoxyribonucleic acid)—A chromosomal constituent of the nuclei of living cells that consists of long chains of nucleotide bases twisted into a double helix and joined by hydrogen bonds; its sequence determines an individual's inherited characteristics.

endocrine glands—Any of various glands or organs, such as the thyroid gland, adrenal glands, and the pancreas, that produce specific substances (hormones), which are secreted directly into the blood or lymph and which act upon other, particular organs. Improperly functioning endocrine glands may cause grave disorders or death.

fetus—The developing young in the uterus after the end of the second month, before which it is called an embryo; it becomes an infant when it is completely outside the body of the mother.

gene—A self-reproducing segment of DNA that makes up a unit of heredity and is located in a definite position (locus) on a particular chromosome. The gene is responsible for the transmission of an inherited characteristic or condition from parents to their children.

hemoglobin—The protein pigment of the red blood cells that carries oxygen to the tissues. Hemoglobin is made up of two parts: heme, which contains iron, and globin chains.

hemoglobin A—The normally predominant type of hemoglobin in the adult; it is either absent or reduced in amount in Cooley's anemia.

hemoglobin A_2—A type of hemoglobin that is present in only limited amounts in the red blood cells of the adult; it is usually increased in amount in beta thalassemia minor.

hemoglobin F—Normally the predominant type of hemoglobin in the fetus and the newborn; it persists in very small amounts after the normal switch to hemoglobin A has taken place, but it is increased in amount in Cooley's anemia.

hormone—A chemical substance, produced in the body, that has a specific effect on the activity of a particular gland or organ.

iron chelator—A chemical or drug that combines with iron and thus enables the body to eliminate the metal. Deferoxamine is the drug used to remove the damaging excess iron that is stored in vital organs as a consequence of the frequent blood transfusions used in the treatment of patients with Cooley's anemia.

platelets—Small cells without nuclei that circulate in the blood and aid in the coagulation of the blood and in the contraction of the blood clot.

pneumococci—Virulent bacteria (*Diplococcus pneumoniae*) that cause lobar pneumonia; they may also cause a serious infection in the blood stream in patients whose immune functions are impaired and who are thus highly susceptible to infections.

red blood cells (erythrocytes)—Cells of the blood that contain hemoglobin and function chiefly to transport oxygen to tissues and organs of the body.

RNA (ribonucleic acid)—A constituent of all living cells that consists of a single-stranded chain of nucleotide bases, the structure and sequence of which determine the order in which amino acids are joined to form specific proteins. Messenger RNA is decreased in amount in Cooley's anemia, which accounts for the inability of the red blood cells in this disorder to produce a sufficient amount of the important hemoglobin A.

stem cell—An early form of cell, found mostly in the bone marrow, from which the cells of the blood and other specialized cells descend.

thalassemia—A group of inherited anemias that are the result of an insufficient production of specific globin chains of hemoglobin. Beta thalassemia major and minor, which are the result of an insufficient production of beta globin chains, are the forms most commonly recognized in the United States. Alpha thalassemia, which is the result of an insufficient production of the alpha globin chains of hemoglobin, is commonly found in the Far East.

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white blood cells (leukocytes)—Cells of the blood that are white or colorless and concerned chiefly with defending the body from infection.

Physicians who are interested in the current status of research and treatment relating to Cooley's anemia may request a copy of *Assessment of Cooley's Anemia Research and Treatment*, DHEW Publication No. (NIH) 79-1653, from the Public Inquiries and Reports Branch; National Heart, Lung, and Blood Institute; National Institutes of Health; Building 31, Room 4A-21; Bethesda, Maryland 20205.

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